

Quetiapine Addition to Serotonin Reuptake Inhibitors in Patients With Severe Obsessive-Compulsive Disorder

A Double-Blind, Randomized, Placebo-Controlled Study

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Objective: Although many patients with obsessive-compulsive disorder (OCD) benefit from treatment with serotonin reuptake inhibitors (SRIs), it is estimated that 40% to 60% of them do not respond. The objective of the present study was to evaluate the efficacy of quetiapine added to baseline treatment with SRIs for the treatment of OCD in severely ill adult subjects.

Method: Forty patients (21 men, 19 women) with primary OCD according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria participated in a 12-week, double-blind, placebo-controlled trial. They were randomly assigned to dosages of quetiapine titrated up to 400 mg/d ($n = 20$) or to placebo ($n = 20$) in addition to their SRI treatment. During the continuation phase (weeks 6–12), subjects received different dosages between 400 and 600 mg/d depending on clinical response. At entry, all patients were unresponsive to at least 1 course of at least 12 weeks of treatment with SRIs at defined doses. The total Yale-Brown Obsessive-Compulsive Scale score was the primary efficacy parameter.

Results: Intention-to-treat, last-observation-carried-forward analysis demonstrated a mean $\pm$ SD decrease in Yale-Brown Obsessive-Compulsive Scale score of 5.2 ± 5.4 in the quetiapine group and 3.9 ± 4.9 in the placebo group. The analysis of treatment effects between the 2 groups showed no significant difference. There were no significant group differences in any of the other self-rating scales or clinician-administered rating scales.

Conclusions: In this study, augmentation of SRI treatment with quetiapine in severe OCD had no additional effect.

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Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder characterized by either obsessions or compulsions that cause significant distress to the afflicted

individual. Serotonin reuptake inhibitors (SRIs) are considered the most effective and well-established pharmacotherapy for the treatment of OCD.¹ However, 40% to 60% of OCD patients do not respond adequately to SRI therapy, and an even greater proportion of patients fail to experience complete remission of their symptoms.¹ Even those patients who are clinical responders (typically, >25–35% decline in Yale-Brown Obsessive-Compulsive Scale [Y-BOCS] rating) continue to experience significant impairment from their residual OCD symptoms. The addition of dopamine antagonists to SRI medication has been implemented to aid OCD patients nonresponding to SRI monotherapy. Reports on placebo-controlled trials of SRI augmentation using haloperidol, risperidone, olanzapine, and quetiapine support further exploration of the efficacy of this approach in treatment-resistant OCD, although negative as well as positive findings have been reported.²

Because OCD patients typically require prolonged pharmacotherapy, the risk of tardive dyskinesia severely limits the use of additional antipsychotic treatment in OCD. Quetiapine has been claimed to be associated with a favorable adverse effect profile compared with other second-generation antipsychotics, with a low propensity for extrapyramidal side-effects, endocrinologic changes, and sexual dysfunction.³ Contradictory results have been obtained from open label^{4–7} and single-blind⁸ studies of quetiapine augmentation in OCD patients. Three double-blind, placebo-controlled studies also yielded inconsistent results. The first randomized controlled study by Denys et al⁹ in 2004 demonstrated that quetiapine (maximum of 300 mg/d) in addition to an SRI is beneficial for patients with OCD who do not respond to SRI treatment alone. In this 8-week study ($n = 40$), 8 of 20 patients (40%) in the quetiapine group and 2 of 20 patients (10%) in the placebo group were responders (defined as Clinical Global Impressions Improvement [CGI-I] Scale¹⁰ scores of 1 or 2 and Y-BOCS¹¹ reduction of >35%).

On the other hand, Carey et al¹² in 2005 and Fineberg et al¹³ in 2005 found no effect of quetiapine augmentation in treatment-resistant OCD patients. In the 6-week study ($n = 41$) by Carey et al,¹² 40% of subjects ($n = 8/20$) on quetiapine (quetiapine mean, 169 ± 121 mg/d) were classified as responders, whereas 47.6% of subjects ($n = 10/21$) on placebo were classified as responders (CGI-I score of 1 or 2; Y-BOCS reduction of >25%). Both the quetiapine group and the placebo group showed significantly improved symptoms of OCD as measured by Y-BOCS scores. The authors argued that this

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improvement is presumably attributable to the continued treatment with selective serotonin reuptake inhibitors (SSRIs) because patients were included in the study only after a minimum of 6 weeks of SSRI treatment. It is reasonable to assume that an effective dose of SSRI had not been obtained before patients were included in the trial. Additionally, Carey et al¹² argued that they did not find any effects of quetiapine because the mean daily dose of quetiapine was relatively low. In the 16-week study ($n = 21$) by Fineberg et al,¹³ 3 of 11 quetiapine-treated patients (quetiapine mean 215 ± 124 mg/d) performed the status of responders (Y-BOCS reduction of $>25\%$) compared with 1 of 10 patients treated with placebo. Fineberg et al¹³ critically argued that they possibly did not find any favorable effects of quetiapine due to the small sample size.

The results from the abovementioned double-blind, placebo-controlled studies^{9,12,13} were pooled and republished as 2 metastudies by Denys et al¹⁴ and by Fineberg et al.¹⁵ These 2 meta-analyses with pooled individual data ($n = 102$) from the previous studies showed that quetiapine addition was superior to placebo. However, in the first meta-analysis by Denys et al,¹⁴ the mean decrease on the Y-BOCS for the quetiapine group (6.8 ± 6.7) was relatively small compared with the decrease in the placebo group (3.9 ± 6.5), which casts doubt on the clinical relevance of these results. Additionally, despite their positive finding for quetiapine, Fineberg et al¹⁵ also state that the clinical significance of their results is questionable. Finally, in a recent systematic review of antipsychotic augmentation in treatment refractory OCD, Bloch et al² found that quetiapine augmentation failed to demonstrate efficacy as compared with placebo. Thus, the efficacy of additional quetiapine augmentation is still questionable.

The primary objective of the present study was to evaluate the efficacy of quetiapine in combination with SSRI or clomipramine (SRI) for the treatment of OCD in adult subjects. We report here on the results of a double-blind, placebo-controlled study of 40 patients who entered a 12-week trial to receive quetiapine or placebo in addition to their current SRI. We aimed to replicate and extend research on the efficacy of quetiapine in severe OCD and to address a number of limitations of previous investigations. In contrast to the Carey et al¹² study, our subjects received relatively high doses of quetiapine (between 400 and 600 mg/d, depending on clinical response). We included only patients who were unresponsive to at least 1 course of at least 12 weeks of treatment with SRIs at defined doses. In contrast to the study by Fineberg et al,¹³ we studied a larger sample size. With these improvements, we hope to increase the chances of finding any effects of quetiapine. Thus, our hypothesis was that there would be a greater reduction in OCD symptoms in the quetiapine group than in the placebo group.

METHODS

Subjects

Forty patients were recruited in 2 centers (University of Luebeck and Freiburg, Germany), gave consent to participate in this study, and signed the informed consent. Both study sites received approval from their Research Ethics Committees. Participants were female or male, aged between 18 and

65 years, who were diagnosed with primary OCD according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria. The diagnosis was confirmed using the Structured Clinical Interview for *DSM-IV*. Only patients with a score of at least 18 on the Y-BOCS¹¹ were included. Patients with comorbid depressive disorder, chronic tic disorder, or Tourette disorder were not excluded. Additionally, to be included, patients had to be treated with an SRI for at least 12 weeks with at least 40 mg/d of citalopram, 175 mg/d of clomipramine, 40 mg/d of fluoxetine, 200 mg/d of fluvoxamine, 40 mg/d of paroxetine, or 100 mg/d of sertraline. Patients were nonresponders to the SRI treatment, defined as less than 25% improvement in Y-BOCS after at least 12 weeks of consistent SRI treatment. All OCD patients from the 2 study centers who met the inclusion criteria were asked to participate in the study.

Female subjects of childbearing potential were required to use adequate contraception. The exclusion criteria were known intolerance or lack of response to quetiapine and current or previous diagnosis of a psychotic disorder, drug or alcohol abuse according to *DSM-IV* criteria, or acute suicidal tendency. Patients with current or previous organic brain disease, epilepsy, or known HIV infection were excluded, as were pregnant or breastfeeding women. Other reasons for exclusion from this study were evidence of clinically significant and unstable renal, cardiovascular, hepatic, hematologic, or endocrine conditions. Taking medication that was deemed likely to interact with quetiapine (potent cytochrome P450 inducers or inhibitors), antihypertensive medication (if doses were not stable for at least 1 month), or any other psychoactive substance were grounds for exclusion. All patients received cognitive-behavioral therapy (CBT) for at least 20 hours before entering the study. Continuation of CBT was allowed, but participants were excluded if they started CBT during the study.

Study Design

Participants were randomly assigned to receive quetiapine or placebo for 12 weeks in addition to their current SRI in a multicenter, double-blind, placebo-controlled, balanced, parallel-group study design. The dose of the SRI was not changed during the 12-week trial. During the first week, all subjects received 100 mg quetiapine or placebo before bedtime. After 3 weeks, the dose was increased weekly in 100 mg/d steps. At the end of the titration phase, every subject received 2×200 mg (morning and evening) of quetiapine or placebo. In the case of unsatisfactory improvement, the dose of quetiapine or placebo could be further increased by 100 mg/d after the sixth and after the eighth week up to a maximum dose of 600 mg quetiapine or placebo per day.

Ratings, Treatment Response, Study Measurements

Patients were evaluated by a psychiatrist or psychologist specialized in the assessment and treatment for OCD at baseline and at weeks 2, 4, 6, 8, 10, and 12. Subjects were rated on the Y-BOCS,¹¹ the Yale Global Tic Severity Scale,¹⁶ the CGI Scale,¹⁰ the CGI-I Scale,¹⁰ the Hamilton Depression Rating Scale (HAM-D),¹⁷ the Ego-Syntonic Scale, the self-rated Patient

Global Impression (PGI) Scale,¹⁰ and the Beck Depression Inventory (BDI).¹⁸ The quality of life of the subjects was measured by Short-Form-36-Questionnaire (SF-36).¹⁹ The primary end point was defined as the absolute change of OCD symptoms from baseline to end point using the total Y-BOCS score. A patient was rated as a responder based on greater than 35% decrease in Y-BOCS score. Physical examination, laboratory values (routine hematology, biochemistry profile), and electrocardiogram were performed at the first visit. Blood pressure, heart rate, and weight were obtained at each visit. Any adverse events reported by the patient or observed by the investigator were documented at each visit. Blood for plasma drug level determination was collected at weeks 0 and 12 for the level of SRIs and at week 12 for the level of quetiapine.

Statistical Analysis

The primary efficacy parameter (Y-BOCS score) was analyzed for all subjects with at least 1 visit after the baseline after an intention-to-treat (ITT), last-observation-carried-forward (LOCF) procedure with Student *t* test. As some studies suggest that the severity of OCD may be better evaluated by considering the Y-BOCS subscales separately,²⁰ we conducted additional analyses on the separate obsessive and compulsive Y-BOCS subscale scores. An analogous procedure was performed for the other clinical outcome measures. Fisher exact test was used to compare the responder rates. The safety analysis was performed using the all-subjects-treated method (AST). The CGI was analyzed using a Cochran-Mantel-Haentzel test (CMH test) adjusting for center.

The data are presented as means $\pm$ SD at a 5% level of significance. All statistical analyses were conducted with the Statistical Package for the Social Sciences for Windows (version 12; SPSS Inc, Chicago, Ill). Out of 40 randomized subjects (19 females, 21 males), 39 took at least 1 dose of study medication and formed the AST population. Two of the forty randomized subjects were excluded from the ITT population because they did not have any postbaseline value on the Y-BOCS total score.

RESULTS

Study Sample Characteristics

Twenty patients were allocated to the quetiapine arm and 20 to the placebo arm. Nine of 39 treated subjects (quetiapine, 6; placebo, 3) discontinued prematurely. The number of non-completers did not differ statistically between the treatment groups (Fisher exact test, $P = 0.273$). Five subjects (quetiapine, 4; placebo, 1) withdrew from the study prematurely due to adverse events (generalized Fisher exact test, $P = 0.347$). Four subjects (quetiapine, 2; placebo, 2) withdrew informed consent and discontinued prematurely. On the basis of the ITT population, no clinically relevant differences between treatment groups were seen with regard to sociodemographic and clinical characteristics. Thirteen of 20 patients (65%) of the placebo group and 8 of 18 patients (44%) of the quetiapine group had a comorbid affective disorder. Two patients of the placebo group and one of the quetiapine group had a comorbid tic disorder. Three patients of the quetiapine group had a comorbid personality disorder. None of the study participants fulfilled the

DSM-IV criterion "OCD with poor insight." On the basis of the AST group, the mean extent of exposure to study drug was 69.1 days in the quetiapine group and 76.6 days in the placebo group.

Global Treatment Response—CGI

After an ITT-LOCF analysis, quetiapine addition demonstrated no significant difference to placebo at the end of the study (CMH test, $P = 0.95$). Four of 18 patients (22%) in the quetiapine group were "much improved," whereas in the placebo group, 6 patients (30%) were rated as "much improved." None of the patients was "very much improved."

Change in Obsessive-Compulsive Symptoms

As measured by the reduction in total Y-BOCS scores, after an ITT-LOCF analysis, quetiapine addition demonstrated no significant difference to placebo at the end of the study, with a mean decrease of 5.2 ± 5.4 and 3.9 ± 4.9 , respectively (Table 1). At end point, 6 patients (33.3%) in the quetiapine group and 3 patients (15%) in the placebo group had a 35% or greater decrease on the Y-BOCS (Fisher exact test, $P = 0.26$). The change from baseline was statistically significant from week 2 onward within the quetiapine group and from week 4 onward in the placebo group. The means of the Y-BOCS obsession subscale and of the Y-BOCS compulsion subscale decreased

TABLE 1. Statistical Analysis (*t* Test) of Various Changes From Baseline to End Point for Various Efficacy Parameters (ITT Population, LOCF)

Parameter	Treatment Group	Baseline, Mean $\pm$ SD	Change Baseline to End Point, Mean $\pm$ SD	Mean Treatment Difference Quetiapine-Placebo	<i>P</i>
Y-BOCS, total score	Quetiapine	24.1 $\pm$ 4.96	-5.22 $\pm$ 5.37	-1.37	0.4163
	Placebo	25.5 $\pm$ 4.14	-3.85 $\pm$ 4.91		
Y-BOCS, obsession scale	Quetiapine	12.8 $\pm$ 2.69	-2.83 $\pm$ 3.31	-0.98	0.3443
	Placebo	12.9 $\pm$ 2.40	-1.85 $\pm$ 3.01		
Y-BOCS, compulsion scale	Quetiapine	11.3 $\pm$ 5.58	-2.39 $\pm$ 3.15	-0.39	0.6976
	Placebo	12.6 $\pm$ 2.40	-2.00 $\pm$ 2.97		
CGI-S	Quetiapine	5.2 $\pm$ 0.65	-0.56 $\pm$ 0.92	0.24	0.3594
	Placebo	5.6 $\pm$ 0.60	-0.80 $\pm$ 0.70		
HAM-D (21 items)	Quetiapine	12.6 $\pm$ 7.90	-1.83 $\pm$ 5.68	0.87	0.6533
	Placebo	15.8 $\pm$ 6.22	-2.70 $\pm$ 6.07		
Ego-Syntonic Scale	Quetiapine	10.4 $\pm$ 2.30	-0.50 $\pm$ 3.35	-0.05	0.9546
	Placebo	9.5 $\pm$ 1.67	-0.45 $\pm$ 1.64		
PGI-S	Quetiapine	5.5 $\pm$ 1.15	-0.72 $\pm$ 1.02	0.38	0.3461
	Placebo	6.0 $\pm$ 1.03	-1.10 $\pm$ 1.37		
BDI	Quetiapine	20.5 $\pm$ 13.8	-4.56 $\pm$ 5.90	0.34	0.8488
	Placebo	19.2 $\pm$ 6.42	-4.89 $\pm$ 4.81		
SF-36, physical factor	Quetiapine	19.8 $\pm$ 12.72	1.36 $\pm$ 6.49	2.59	0.2397
	Placebo	18.6 $\pm$ 7.07	-1.24 $\pm$ 5.54		
SF-36, mental score	Quetiapine	33.1 $\pm$ 11.17	-2.07 $\pm$ 7.75	2.93	0.3227
	Placebo	35.9 $\pm$ 5.38	-5.00 $\pm$ 8.44		

over time in both treatment groups, indicating an improvement during the treatment period. However, no statistically significant differences between the treatment groups were found at any time-point.

Change in Other Outcome Measures Administered by Clinicians

No statistically significant differences between the 2 treatment groups were seen in the changes from baseline to end point in the parameters HAM-D total score [21-items], CGI-S, or Ego-Syntonic Scale (Table 1) at any time point. Only 1 patient experienced a comorbid tic disorder with a relevant score in the Yale Global Tic Severity Scale, so we did not conduct any statistical analysis.

Change in Patient-Reported Outcome Questionnaires

Mean scores from the patient-reported outcome parameters BDI and PGI of severity scale (PGI-S) showed no statistically significant differences during the course of the study. At

end point, no statistically significant treatment differences were found in either of the 2 parameters or in the SF-36 physical and mental scores (Table 1).

Tolerability of Quetiapine, Dropouts, and Plasma Drug Concentrations

All treated patients reported at least 1 adverse event during the 12 weeks of treatment. Most subjects had 5 and more adverse events. The most frequent ($\geq 10\%$ in overall sample) side effects are presented in Table 2. The most prominent side effects—based on preferred terms from MedDRA V.9.1—were “fatigue,” “headache,” “hyperhidrosis,” “vertigo,” and “dry mouth.” Drug-related adverse events were experienced by 19 patients (100%) from the quetiapine group and 11 patients (55%) from the placebo group. Severe adverse events (SAEs) were documented for 1 patient in the quetiapine group and 3 patients in the placebo group. The subject from the quetiapine group experienced “increased cardiac enzymes,” whereas the subjects from the placebo group experienced “orthostatic collapse,” “cramps in lower abdomen,” and “headache.” All SAEs except “cramps in lower abdomen” were considered to be drug-related by the clinicians. Plasma levels of quetiapine and SRI were obtained mainly to confirm compliance.

DISCUSSION

The objective of the present study was to evaluate the efficacy of quetiapine in combination with SSRI or clomipramine (SRI) in severely ill adult OCD patients. Forty OCD patients participated in a double-blind, placebo-controlled study and entered a 12-week trial to receive quetiapine or placebo in addition to their current SRI. The main results demonstrate an average decrease of Y-BOCS means of 5.2 (22%) in the quetiapine group and of 3.9 (15%) in the placebo group after 12 weeks of treatment. However, the difference between the groups did not reach significance either at the end of treatment or at any other time during the study. Additionally, there were no significant differences in any other variables including self-ratings and clinician-administered ratings, such as ratings of the obsessive-compulsive symptoms, the depressive symptoms, the ego-dystonia of the obsessive symptoms, and the quality of life. Results were inconsistent with hypothesis because we had expected that the patients treated with additional quetiapine would improve more than those treated with placebo. Thus, our results support previous studies showing that augmentation with quetiapine has no additional effect in OCD patients who did not respond to a 12-week SRI treatment alone.

Comparison With Similar Trials

Our study supplements and extends the results of Carey et al¹² and Fineberg et al¹³ who also did not find any additional effects of quetiapine. In contrast to Carey et al,¹² our subjects received relatively high doses of quetiapine (between 400 and 600 mg/d, depending on clinical response), thereby increasing the chances of finding any effects of quetiapine. In contrast to the study by Fineberg et al,¹³ we studied a larger sample size of $n = 40$ patients. The fact that we *still* did not obtain significant differences between quetiapine and placebo strongly supports the hypothesis that adjunctive quetiapine is not effective in OCD.

TABLE 2. Overview of Adverse Events, Including Most Frequently Reported Side Effects ($\geq 10\%$; ie, 4 Patients in Overall Sample), AST Population

	Quetiapine, n = 19		Placebo, n = 20		P
	n	%	n	%	
Overview about adverse events					
Subjects with at least 1 AE	19	100%	20	100%	n.d.
Subjects with at least 1 SAE	1	5%	3	15%	n.d.
Subjects with at least 1 drug-related AE	19	100%	11	55%	n.d.
Subjects with at least 1 drug-related SAE	1	5%	2	10%	n.d.
Most frequently (≥10% in overall sample) reported adverse events					
Fatigue	17	90%	13	65%	0.1274
Headache	7	37%	11	55%	0.3406
Hyperhidrosis	6	32%	10	50%	0.3332
Vertigo	9	47%	5	25%	0.1908
Dry mouth	10	53%	3	15%	0.0187*
Abdominal pain upper	3	16%	5	25%	0.6948
Dyspepsia	7	37%	1	5%	0.0197*
Influenza-like illness	1	5%	6	30%	0.0915
Constipation	5	26%	1	5%	0.0915
Diarrhea	1	5%	5	25%	0.1818
Disturbance in attention	5	26%	1	5%	0.0915
Nausea	2	11%	4	20%	0.6614
Increased appetite	3	16%	3	15%	1.0000
Apathy	3	16%	2	10%	0.6614
Nasopharyngitis	1	5%	4	20%	0.3416
Dizziness	3	15%	1	5%	0.3416
Nightmare	2	10%	2	10%	1.0000

The adverse event description is based on the preferred term from MedDRA V. 9.1.

P values (two-sided) are based on Fisher exact test.

*indicates statistically significant difference.

n.d. indicates not done.

On the other hand, our results are inconsistent with the first double-blind, placebo-controlled study of augmentation with quetiapine (maximum of 300 mg/d) by Denys et al.⁹ One possible explanation for this discrepancy is that, in contrast to all previous double-blind, placebo-controlled studies of quetiapine augmentation, we included OCD patients with co-existing Axis I or II diagnosis. Most of the participants had at least 1 comorbid disorder (mean 1.2), like an affective, anxiety, or personality disorder. It is therefore possible that OCD patients without any comorbid disorder benefit from quetiapine, whereas those with at least 1 additional psychiatric disorder do not. However, taking into account that most OCD patients have at least 1 comorbid disorder, our study provides a higher ecological validity, and results are more likely to be generalizable to other OCD patients. Additionally, we included only patients who were unresponsive to courses of at least 12 weeks of treatment with SRIs at a defined minimum dose. Improvement effects over time in both groups are therefore unlikely to be attributable to the continuous effects of SRIs. Instead, it is reasonable to assume that (long-term) effects of psychotherapy (exclusively CBT) became effective over and above the pharmacological treatment.

Evidence regarding the efficacy of quetiapine augmentation in treatment-resistant OCD remains inconclusive. Further research is needed into the impact of quetiapine augmentation and any specific efficacy it may have. Clinical implications are that quetiapine augmentation cannot be recommended as the standard procedure for OCD patients who do not respond to SRI treatment. Future studies should therefore also consider alternative pharmacological approaches and explore findings on the efficacy of other atypical antipsychotics. Alternatively and additionally, psychiatric treatment procedures for refractory OCD patients should include extended CBT provided over sufficient time and including essential interventions such as exposure and response prevention, preferably in the relevant context in which obsessions and compulsions actually occur.

Limitations

One limitation of the present study is a relatively high dropout rate. Six patients did not continue with the treatment of the total of 12 weeks in the quetiapine group, and 3 patients did not continue in the placebo group. This dropout rate was slightly higher than in previous quetiapine augmentation studies. Most dropouts in the quetiapine group occurred due to adverse events, which are possibly attributable to the higher dose of quetiapine compared with previous studies.

CONCLUSIONS

In this study, the addition of quetiapine to a treatment with SRIs (SSRI or clomipramine) in patients with severe OCD had no beneficial effects in a randomized double-blind, placebo-controlled 12-week trial. On the basis of the study's results, quetiapine augmentation cannot be recommended as a first-line strategy in OCD patients with at least 1 insufficient SRI treatment response. However, quetiapine was generally well tolerated in this patient population.

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